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Prediction of coronary heart disease: a comparison between the Copenhagen risk score and the Framingham risk score applied to a Dutch population

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Abstract. de Visser CL, Bilo HJG, Thomsen TF, Groenier KH, Meyboom-de Jong B (University of Groningen, Groningen; Isala Clinics, Weezenlanden location, Zwolle, The Netherlands; Glostrup University Hospital, Glostup, Denmark). Prediction of coronary heart disease: a comparison between the Copenhagen risk score and the Framingham risk score applied to a Dutch population. *J Intern Med* 2003; **253**: 553–562.

Objectives. To compare the estimation of coronary heart disease (CHD) risk by the Framingham risk score (FRS) and the Copenhagen risk score (CRS) using Dutch population data.

Design. Comparison of CHD risk estimates from FRS and CRS. CHD risk-estimations for each separate risk factor.

Setting. Urk, the Netherlands.

Subjects. A total of 408 fishermen from Urk, aged 30–65 years, without pre-existing cardiovascular disease.

Main outcome measures. Absolute CHD risk estimates.

Results. The average 10-year risk for CHD was significantly different between the FRS (4.6%, SD 5.0) and the CRS (3.2%, SD 4.1). The correlation between the two estimates was 0.94 ($P < 0.001$). The Bland–Altman figure shows a large proportion of agreement, but with an increasing difference with increasing average risk. When examining the separate risk factors age, total cholesterol, HDL cholesterol and systolic blood pressure and smoking, there appear differences between the two risk functions.

Conclusion. Using Dutch population data, differences were found for the calculation of CHD risk with the FRS and the CRS. Further research must be carried out to examine the validity of these risk functions in the Dutch population.

Keywords: coronary heart disease, Netherlands, prevention, risk assessment, risk factors.

Introduction

Various studies have shown that the risk for coronary heart disease (CHD) is determined by a number of risk factors and their interactions. The most important factors are age, gender, smoking, blood pressure, cholesterol level and diabetes mellitus [1–3]. The major established risk factors explain approximately 75% of the occurrence of CHD within populations [4].

Accurate estimation of the absolute risk is not always straightforward. Physicians understand the relative importance of the various risk factors, but

they tend to overestimate the absolute risk when assessing individual patients [5, 6]. The total risk for CHD is best estimated by considering the cumulative effect of various risk factors [7]. For optimal calculation of the risk for CHD, multivariate techniques have been used to develop so-called 'risk scores'. A risk score is a mathematical formula reflecting the relationship between the risk factors and the incidence of specific end-points. Risk-scores make it possible to calculate both the absolute and the relative risks for different cardiovascular disease (CVD) outcomes. Risk scores are an important tool for prevention and also in allowing for a

re-evaluation of risk when changes in the risk profile occur. The risk calculation from the Framingham Heart Study is most often used [7].

In practice, calculating the risk for CHD and CVD is important in identifying high-risk patients, motivating patients for intervention, and generating a risk profile when assessing the indication for pharmaceutical treatment in primary prevention of CVD. Assessment of absolute risk for CHD and CVD has become an accepted basis for the use of cholesterol-lowering drugs and the use of antihypertensive agents [8–20]. Absolute risk assessment is also needed to calculate the number needed to treat (NNT) and to evaluate the cost-effectiveness of treatment, and to assess the populations implications of treatment policies based on random control trail evidence [21].

In the clinical guidelines, the indication for treating hypercholesterolaemia is generally based on the absolute risk for CHD, whilst for hypertension the general risk for CVD is used [9, 10, 19, 20, 22].

Although there is widespread acceptance amongst Dutch family physicians of the national guidelines, it has been documented that the guidelines are used only partly or not at all in actual practice situations [23]. The implementation of these guidelines may become more universal when physicians are offered practical and efficient methods for informing and motivating their patients, thereby improving their insight. Translating the theoretical chance of disease into realistic conceivable realities for the patient is one of the most important practical problems faced by physicians [24]. As the simplicity and quality of CVD risk calculation methods increase, treatment implementation becomes more efficient. Furthermore it is supposed that when evaluating the indication for treatment with antihypertensive medication, efficiency could be increased when an absolute risk calculation for CVD is used [25].

For rational use, clinicians need to be confident that absolute risk predictions can be transported to other settings beyond where they were originally developed. To assess the applicability of risk predictions to other populations, it is important to look at the distribution, incidence and impact of the different risk factors and the incidence of defined endpoints. Possible variations, occurring amongst the different populations, must be examined and taken into account [26, 27].

Recently, a European risk calculation program, named PRECARD®, was developed in Denmark [28]. PRECARD® calculates the absolute and relative risks for CHD, and also the expected efficacy of any interventions. The PRECARD® program uses the Copenhagen Risk Score (CRS) to calculate the absolute risk for CHD. PRECARD® also generates an individualized patient-focused health advice.

In the present study, the absolute CHD risk estimate of the CRS is compared with the risk estimate of the Framingham Risk Score (FRS) as currently used in various European cardiovascular guidelines. Using Dutch population data, the results obtained with the two absolute risk calculations are compared, and the risk assessments per individual risk factor are examined.

Material and methods

To be able to study the difference in outcome of the risk assessment of the CRS and the risk calculation used in the FRS, both calculations were applied to data on a population of fishermen from Urk. Urk is a former island in the Netherlands, with a large population of North Sea fishermen. Data on major cardiovascular risk factors were gathered since 1989 during the obliged annual check-up. These data were and are used to study the prevalence of cardiovascular risk factors and to study longitudinal changes. The methods and the study design have been described elsewhere [29]. For the risk calculation, data from 406 men aged 30–65 years were used, from whom all pertinent information was known. The general characteristics for this population are summarized in Table 1.

In the PRECARD® program, the CRS is used to calculate the absolute risk for myocardial infarcts (MI), CHD, cerebrovascular disorders and total mortality. The CRS is based on the results of 11 765 individuals from two large Danish studies, the Glostrup Population Study and the Copenhagen City Heart Study, with a total of 120 000 person-years. The Cox regression model was used to analyse the data, with age as time variable. One of the limitations of the CRS is that the risk for CHD, cerebrovascular disorders and overall mortality can be reliably measured only for individuals aged 30–70 years, who have an annual risk between 0.5 and 4.0%. As is true for all risk scores, the accuracy of the risk calculation is limited when a patient's risk

Table 1 General characteristics of the study population

	Mean (SD) or n (%)
Number	406
Age (years)	41.2 (8.0)
Smokers (number of men)	217 (53.4%)
Ex-smokers (number of men)	114 (28.1%)
Positive family history (number of men)	102 (25.1%)
Prior coronary heart disease (number of men)	0
Diabetes mellitus type 2 (number of men)	7 (1.7%)
Body mass index (kg m^{-2})	28.4 (3.7)
Systolic blood pressure (mmHg)	140 (19)
Total cholesterol (mmol L^{-1})	6.3 (1.2)
HDL cholesterol (mmol L^{-1})	1.17 (0.31)

Table 2 Variables of the Copenhagen and Framingham Risk Scores

Copenhagen Risk Score	Framingham Risk Score
Non-modifiable risk factors	
Age	Age
Gender	Gender
Diabetes mellitus	Diabetes mellitus
Genetic predisposition	–
Previous coronary heart disease	–
–	Left ventricular hypertrophy on ECG
Modifiable risk factors	
Smoking	Smoking
Total cholesterol	–
HDL cholesterol	–
–	Total/HDL cholesterol
Body mass index	–
Systolic blood pressure	Systolic blood pressure

factors are exceedingly high or low. The risk score is therefore not recommended for such patients.

The FRS described by Anderson *et al.* is used as comparison in the presented study, because it is used as a risk assessment instrument in many protocols throughout Europe [7]. This risk score is based on data from the Framingham Heart Study, a longitudinal American study, initiated in 1948 and involving 5209 individuals. Data regarding their cardiovascular risk factors and any development of CVD have been, and are currently still being collected. Using these data, risk scores were developed, with which the risks for CHD, cerebrovascular disorders and CVD can be calculated. The FRS is based on data collected during 12 years of follow-up on the original Framingham cohort and on the Framingham offspring cohort [7]. Recently new sex-specific models for primary and secondary CHD have been produced [30, 31]. The FRS is often preferred, as its calculations are based on an extensive data collection, and because it offers the possibility of calculating the risk for CHD, cerebrovascular and CVD for both men and women aged 30–74 years. The FRS is available for practical usage in card, tabular and computer format.

Simplified forms of the FRS by Anderson *et al.* have been incorporated in European, New Zealand, UK and Dutch national guidelines for the management of hypercholesterolaemia and hypertension [9–18]. This risk score is based on a parametric regression model to provide predicted probabilities for CHD.

In Table 2, an overview is given of the risk factors, which are used for the CRS and the FRS. In our study, no information was available about left ventricular hypertrophy on electrocardiogram (ECG). In the calculation for all individuals, this variable was therefore considered negative.

The definitions for CHD used for the CRS and the FRS are different [7]. The CRS uses a definition for 'hard' CHD, which includes fatal and nonfatal MI. The FRS provides estimates of total CHD and includes angina pectoris and coronary insufficiency in addition to the two aforementioned conditions. Generally, estimates for 'hard' CHD are about two-thirds to three-fourths of those of total CHD [20]. To make the two risk estimates comparable with regard to end-point definition, the approximate equivalency for 'hard' CHD per age-category have been calculated for the FRS (modified from Wilson *et al.*) [31].

For each individual, the estimated CHD risk was calculated by each risk function, using the variables required and expressed as a percentage per 10 years. The comparison involves studying the convergent validity of the CRS to the FRS. This means that it was determined whether or not the results obtained with the CRS calculation are consistent with the results obtained using the FRS.

The Student's *t*-test for paired evaluations was used to compare the results obtained with the two risk calculations. The regression coefficients of the risk estimates with the associated 95% confidence intervals were calculated. The estimates for both calculations are presented graphically. The 'line of identity' and the regression line are indicated in the

figure. The 'line of identity' represents the situation which would occur when identical results were obtained with the two methods. The correlation between the two risk calculations was analysed using the method described by Bland and Altman [32].

To discover differences in the risk estimates per separate risk factors, figures were generated, which show the risk estimate resulting from the two methods for the continuous variables such as age, total cholesterol, HDL cholesterol and systolic blood pressure. In these figures, the moving average is calculated so that fluctuations, caused by a small number of observations, are filtered out. For the categorical variable 'smoking', a box-plot shows the risk estimation for the two risk functions for both smokers and nonsmokers.

Results

The average risk for CHD, as calculated with the CRS, is 3.2% (SD 4.1) for 10 years, with a lower limit of 0.1% and an upper limit of 32.4%. The median value is 1.8% for 10 years. The average risk as calculated with FRS is 4.6% (SD 5.0) for 10 years, with a lower limit of 0.1% and an upper limit of 28.4%. The median is 2.9% for 10 years. The average difference between the two risk estimates is 1.4% (SD 1.8) for 10 years, with a lower limit of −4.1% and an upper limit of 8.3% and a median of 0.9% for 10 years. There is a significant ($P < 0.001$) difference between the two risk estimates, although the correlation between the two is high ($r = 0.94$, $P < 0.001$).

The risk estimates, derived from the two methods, are presented in Fig. 1(a). The deviation of the regression line from the line of identity is significant for the intercept (−0.23, 95% confidence interval −0.26 to −0.20) and for the slope (−0.35, 95% confidence interval − 0.54 to −0.16) (Fig. 1a). The risk calculated with the FRS is globally 1.3 more than the risk calculated with the CRS.

The Bland–Altman figure shows the amount of agreement between the two measures (Fig. 1b). A large portion of the calculated differences falls between two standard deviations from the average difference. There is, however, a systematic difference between the two measures, which becomes larger with a higher risk estimate. This is represented as an increase in the difference associated with an
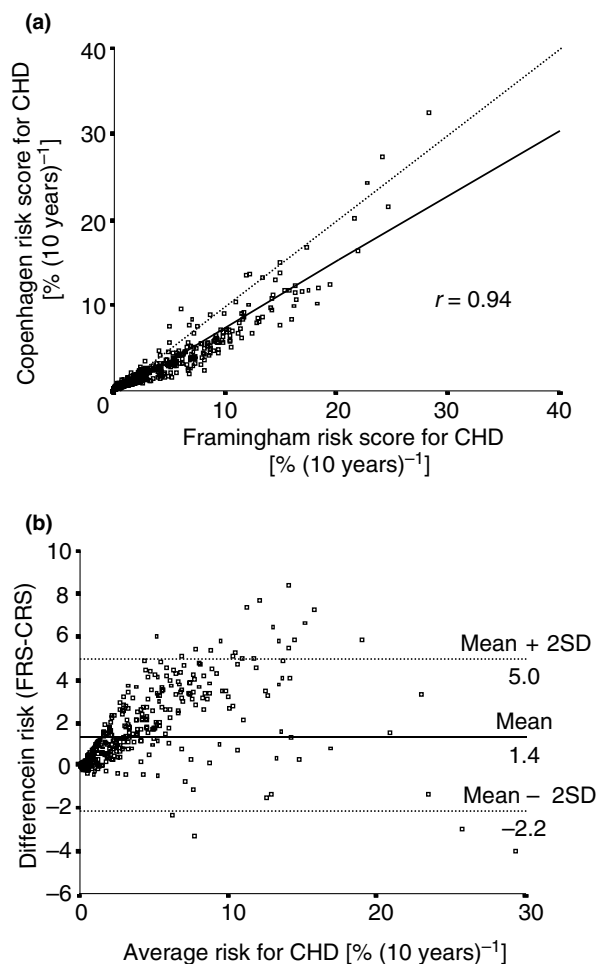

Fig. 1 Risk estimate for coronary heart disease according to the Framingham Risk Score versus the Copenhagen Risk Score. (a) Dashed line = line of identity; solid line = regression line (b) Bland-Altman plot.

increase of the average risk. The variability (range) of the difference increases as the average risk increases.

It can be concluded, that the two measures do not completely agree throughout the spectrum of the risk estimation. The correlation between the difference and the average risk estimate is 0.51, which indicates that the difference increases, when the average risk estimate increases [33].

In Fig 2a–e, risk estimates are presented for each risk factor individually. The figures show how it becomes apparent, that the differences between the CRS and the FRS are determined by all studied variables. Higher risk estimates for the FRS compared with the CRS are seen, when the variables
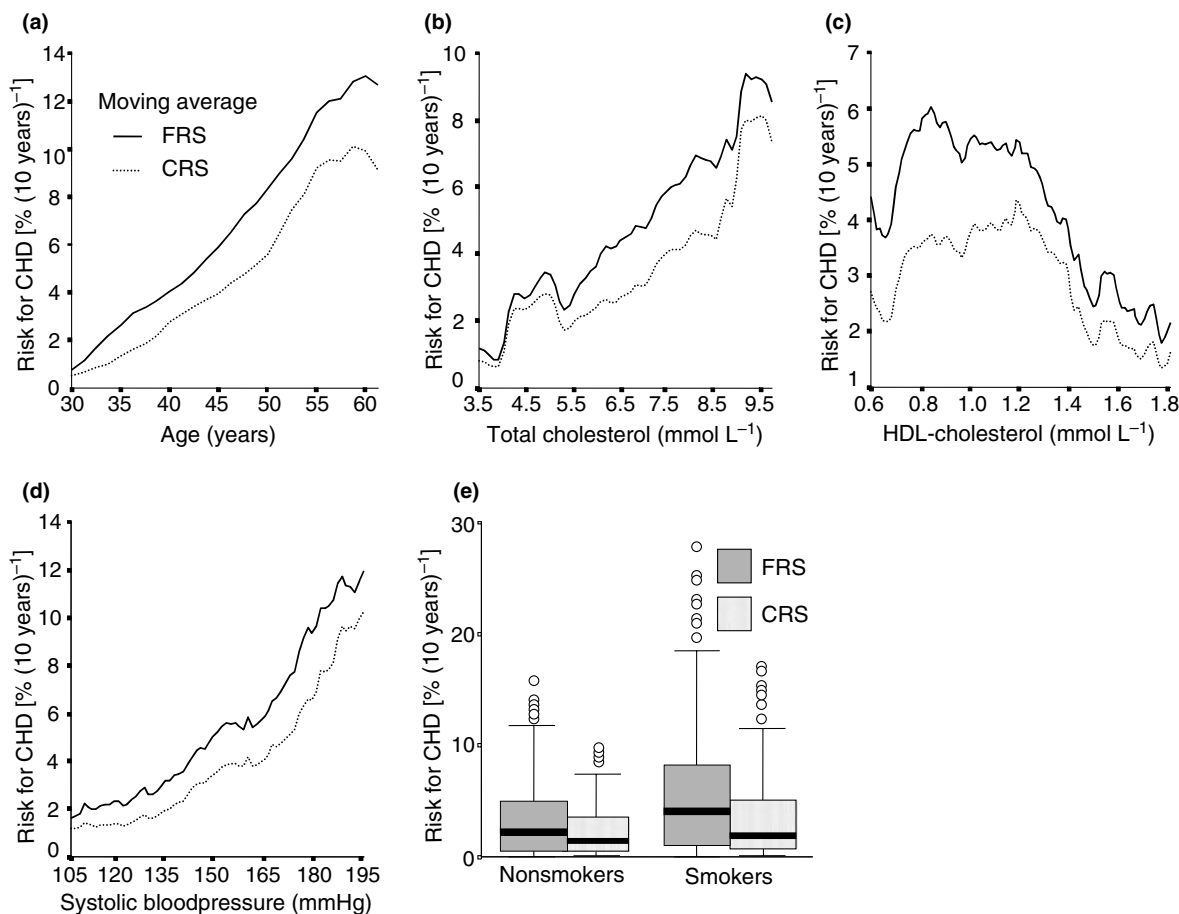
Fig. 2 Risk estimates for coronary heart disease with the Framingham and Copenhagen risk scores for each individual risk factor. (a) age; (b) total cholesterol; (c) HDL cholesterol; (d) systolic blood pressure; (e) smoking.

age, systolic blood pressure, total cholesterol, HDL cholesterol and smoking are considered.

Discussion

This comparison between the CRS, which is the risk assessment used in the PRECARD® program, and the FRS shows, that there are clear differences between these two methods for calculating absolute CHD risk in a Dutch population. Although there is a high correlation between the two risk calculations, the CRS results in a lower absolute risk estimate than the FRS. The difference between the two risk calculations becomes larger with a higher risk estimate. A difference between the two calculations was seen when the variables age, systolic blood pressure, total cholesterol, HDL cholesterol and smoking were examined.

The FRS by Anderson *et al.* used in this comparison has been adopted in various European countries, in accord with guidelines of European cardiovascular societies. The FRS provides estimates of total CHD, whilst the CRS gives risk estimates for only 'hard' CHD end-points (MI and CHD death) [7]. To compare the risk estimates of the FRS with the CRS, the risk estimations of the former were adjusted to approximate equivalents for 'hard' CHD. The adjustment of end-points may have influenced the results. It is however questionable whether the problem with end-points definitions can explain the difference in risk estimation between the two used risk scores. Haq *et al.* compared risk estimations from the Framingham, prospective cardiovascular Münster (PROCAM), Dundee and British regional heart study (BRHS) in a high-risk group of hypertensive men [21]. Although a difference in total and
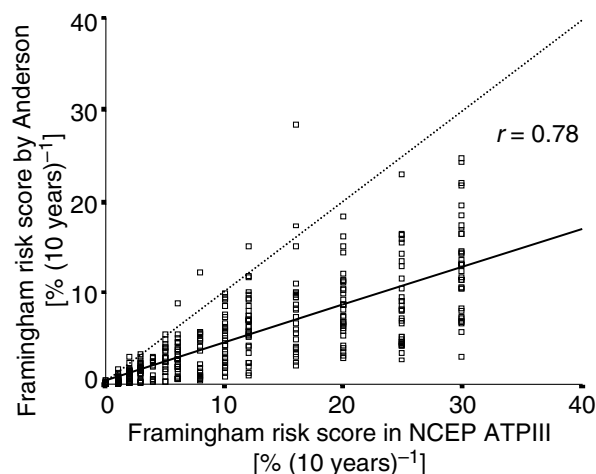
'hard' CHD end-points was applicable between, respectively, the Framingham and the other populations, close agreement was found between the Framingham, PROCAM and Dundee risk functions. This indicates that in our study, explanations other than the differences in end-points might also account for the found results.

Recently, a new Framingham risk scoring specifically applied to 'hard' CHD is described in the National Cholesterol Education Program Adult Treatment Panel III Report (NCEP ATP III) [20]. This risk scoring derives from an update of the Framingham database and methodology reported by Wilson *et al.* [20, 30]. Ten-year absolute CHD risk is assessed with a point scoring system using categorical variables. Comparison of this new risk score with the CRS shows large differences in the risk estimates for 'hard' CHD (Fig. 3). The risk estimates of the new risk score are also clearly out of line with the FRS by Anderson *et al.* if adjusted for 'hard' CHD end-points (Fig. 4). The reason for the overestimation in this new FRS is unknown at present. Exact prediction equations should therefore be provided as soon as possible (as they have not been published yet), so that details can be inspected.

Another supposed explanation for the differences is the difference in risk factors used. The CRS
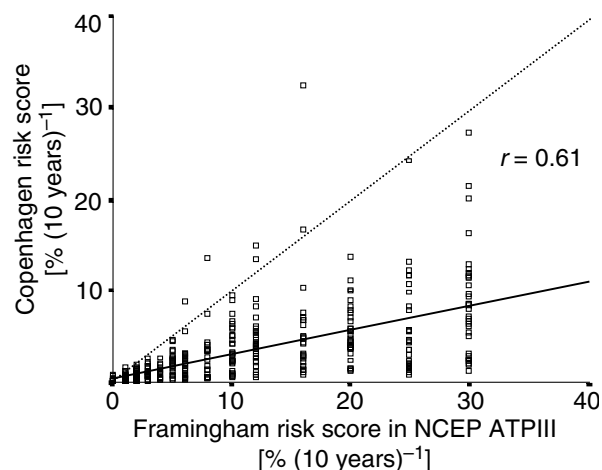
Fig. 4 Risk estimates for coronary heart disease with the Framingham Risk Score in the NCEP ATP III Report versus the Framingham Risk Score by Anderson *et al.* (1990), adjusted for 'hard' CHD. Dashed line = line of identity; solid line = regression line. Mean CHD risk (%/10 years) by Framingham Risk Score (NCEP ATP III): 10.4 (SD 9.4). Mean CHD risk (%/10 years) by Framingham Risk Score (Anderson *et al.*, 1990): 4.6 (SD 5.0).

considers total cholesterol and HDL cholesterol separately, and includes the variables ex-smoker, family history for CVD, and body mass index (BMI). In the FRS, the ratio of total cholesterol/HDL cholesterol and left ventricular hypertrophy, identified on ECG, are used.

Differences between the populations on which the risk functions are based, might be a third explanation for the difference in the risk estimates. The CRS is based on data gathered since 1977, in Denmark, Europe, whereas the FRS is based on older data gathered since 1968 in the United States of America. There has been a dramatic decline in mortality from CHD over the past decades (also in the United States), apparently as a result of a decline in the incidence of individual risk factors and from prevention efforts. Therefore, different predictive coefficients may result from the two studies, as a consequence of changing trends in population risk-factor levels and CHD-event rates. The difference in the incidence of CHD between the two populations may also influence the absolute risk estimate. Sans *et al.* showed that in the period 1990–92, the age-adjusted mortality for CHD in men in the Netherlands was 315 per 100 000 per year compared with 423 per 100 000 per year in Denmark [34].

Fig. 3 Risk estimates for coronary heart disease with the Framingham Risk Score in the NCEP ATP III Report versus the Copenhagen Risk Score. Dashed line = line of identity; solid line = regression line. Mean CHD risk (%/10 years) by Framingham Risk Score (NCEP ATP III): 10.4 (SD 9.4). Mean CHD risk (%/10 years) by Copenhagen Risk Score: 3.2 (SD 4.1).

Thomsen *et al.* found a CHD mortality of 627 per 100 000 person-years in the Framingham population compared with 385 in the Danish Glostrup population [35].

Various studies have shown that the important risk factors for CHD are the same for most populations [36]. However, using the relationship between cardiovascular risk factors and CHD is too heterogeneous to be applied equally to populations differing in ethnic origin [26]. Support for this claim could be found in our study, when the differences between the absolute risk calculations with respect to the factors such as age, systolic blood pressure, total cholesterol, HDL cholesterol, and smoking were considered. However, traditional experience in comparing population groups belonging to different cultures shows that the relative risk bound to different levels in risk factors is similar across cultures, whilst the absolute risk can be very different [37]. A recent study examining the generalizability of risk functions from diverse populations, found that the prediction of absolute risk was not very accurate in most of the cases, when a model derived from one study was applied to a different study [38]. This was also found in a study by Menotti *et al.* [39]. They based risk functions on data obtained from North European and South European countries, and made a comparison. The relation of risk factors to events had a similar trend across the different populations. However, when the North European model was used to examine the South European population, the absolute risk estimation was too high (ratio of about 1.5), and when the South European model was applied to the North European population, the absolute risk estimation was too low (ratio of about 0.5). Using a correction factor for the differing incidences would improve the accuracy of the estimation when the same model is used in different cultures.

Finally, the difference between the outcomes of the comparison of the two risk scores, in total and for the separate risk factors, may be explained by the difference in analysis methods upon which the calculations are based. The CRS is based on Cox's regression model, whilst the FRS is based on a parametric statistical model.

In a study by Thomsen *et al.*, a cross validation of risk scores for CHD based on data from the Glostrup Population Studies and the Framingham Heart Study was made [35]. They found that the risk scores correctly ordered the risk of the individuals in the other population. Although there are clear differences in the general risk profiles between the Glostrup and the Framingham populations, the relative risks are not significantly different. However, the risk score based on the Framingham data significantly overestimated the absolute CHD risk in the Glostrup population and vice versa. Schroll and Larsen compared the coefficients of one cohort of the Glostrup Population Study to the Framingham Heart Study and found the Framingham coefficients to be generally higher [40]. The differences in risk estimates found in our study, were not only caused by differences in end-point definitions, used risk factors and analysing methods, but can also be explained by differences in the incidence of CHD and differences in the relationship between risk factors and absolute CHD risk.

The European treatment guidelines for hypercholesterolaemia and hypertension are based on absolute risk calculations, which use the Framingham risk function [8–19]. The result of the comparison of the American and the European data sets discussed above reveals a marked difference between these two absolute risk calculations. Using the CRS instead of the FRS for diagnostic and treatment indications would result in large differences. This raises the question: which risk calculation can be most reliably used for the Dutch population?

Already different research results which examine the validity of the FRS for different populations have been reported. Most studies report an overestimation of the absolute risk, but a relative risk estimation of reasonable accuracy shows that the relative importance of these risk factors is similar in several populations. In the Seven Countries Study, Keys *et al.* report that the FRS overestimates the risk for CHD [41]. Orford *et al.* found the Framingham prediction model to underestimate absolute risk of CHD in low-risk and overestimate in high-risk subjects of the Normative Ageing Study [42]. A study of D'Agostino *et al.* showed that the FRS overestimated risk in some ethnic groups, and recalibration for risk-factor prevalence and CHD incidence rates corrected this [43]. Several studies have shown that the FRS tended to overpredict absolute risk in populations with a low observed CHD mortality, and underpredict in populations with a high CHD mortality [38, 44]. However, a

study by Haq *et al.* revealed that using data on English hypertensive men, calculation of the average risk for CHD with the FRS is largely in agreement with calculations using the German PROCAM and the English DUNDEE risk score [21]. Recent research conducted by Ramachrandran *et al.* has demonstrated that the absolute risk estimate for CHD as calculated with the FRS for English individuals is reliable when the yearly risk is more than 1.5%. When this risk is less than 1.5%, the FRS underestimates the absolute risk [45]. It was concluded that the accuracy of the risk estimate according to the FRS and its modified derivatives, seems to be acceptable for some North European populations. Nevertheless, as of yet, no results are available for reporting the validity of the application of the FRS to assess the Dutch population.

Likewise, little is known concerning the reliability of risk estimates using the CRS for other populations. It may be reasonable to assume that the lifestyle characteristics of the Dutch population have more in common with the Danish population than with the American population, upon which the FRS is based. This also accounts for the CHD mortality. This difference mentioned above indicates that, concerning the CHD mortality, the Dutch population is more comparable with the Glostrup population than with the Framingham population.

The presented study used data from a population of men with high risk factor levels [29]. All men have the same profession and nationality, which may limit generalizability to some extent. However, the results are relevant to general practice, as because of their high risk factor levels, this group of men is likely to be comparable with those who are screened in primary care for prevention of CHD. Therefore this group of men is an appropriate selection to be used to evaluate risk estimations, rather than selected groups with higher risks based on hypertension, lipid disorders, diabetes or subsequent CHD.

In this study, no data on cardiovascular risk factors in women were available.

Our study did not intend to assess whether the FRS and CRS are accurate in the tested population. To study this, Dutch population data on CHD events rates over time are needed, which are currently not available. However, both the FRS and the CRS are developed to be used in Northern European populations and should therefore be suitable to be used in the Dutch population [45]. As differences in risk estimations were found, the question does present itself whether a risk calculation based on Danish population or Northern American data would be more accurate for the Dutch population. The results of the present comparison invite further research by examining the external validity of risk calculations for the Dutch population and testing them against a risk function based on Dutch population data. The accuracy of absolute risk prediction, particularly at the extremes of multivariate risk, may be questionable and validation of these risk functions is important in the light of the profound impact of these estimates on the management of individual patients and the allocation of community resources.

Conflict of interest statement

No conflict of interest was declared.

Acknowledgement

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